federal register

Tuesday
December 30, 1980

Part XI

Department of Health and Human Services

Food and Drug Administration

Infant Formula Quality Control Procedures; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 106

[Docket No. 80N-0025]

Infant Formula Quality Control Procedures

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: In accordance with the Infant Formula Act of 1980 (Pub. L. 96-359; 94 Stat. 1190), the Food and Drug Administration (FDA) is proposing to establish a new Part 106 (21 CFR Part 106) that requires quality control procedures for the manufacture of infant formula products. The proposed regulations specify a systematic procedure of sampling, testing, analyses, and recordkeeping for in-process and finished formulas and require manufacturers to establish the following: an acceptance protocal for ingredients assuring that they conform to strict specifications for composition and purity; and in-process operational control program of ingredient addition, blending, homogenization, and standardization; and a finished product evaluation system that specifies sampling frequency and an analytical format that defines product release ranges at which the product may be shipped. This proposal ensures that infant formula products contain the necessary nutrients at the specified levels as required by the Infant Formula Act of 1980.

DATES: Comments by March 2, 1981. Proposed compliance date for all affected products initially introduced or initially delivered for introduction in interstate commerce or prepared from raw materials shipped in interstate commerce is 180 days after date of publication of the final regulation.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fisher Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: F. Edward Scarbrough, Bureau of Foods (HFF-204), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-245-3117.

SUPPLEMENTARY INFORMATION: In 1978 a major manufacturer of soy protein-based infant formulas reformulated two of its products. The reformulation resulted in products containing an inadequate amount of the essential nutrient, chloride. By 1979 a substantial number of cases concerning a medical disorder, known as hypochloremic metabolic alkalosis, were reported. This serious medical condition is most frequently characterized by the infant's failure to thrive. These cases of infant illness were found to be associated with prolonged exclusive use of the chloride-deficient soy formulas. This incident made it clear that greater regulatory control over the formulation and processing of infant formulas was necessary.

In response to the chloride-deficient soy formula occurrence, the Commissioner of Food and Drugs contacted members of the infant formula industry requesting information concerning quality assurance and quality control procedures and nutrient analytical methodology. After the submission of these data, the agency, held an open public meeting and an informal public hearing on the general issues of infant formula processing, testing, composition, and safety (see the **Federal Register** of January 29, 1980; 45 FR 6702). The meeting was conducted in Washington, DC on February 19, 1980, to obtain public comment on the issues of open date labeling, quality control and quality assurance practices, and clinical testing needs for infant formulas. The hearing, also in Washington, DC, was conducted on March 12, 1980, and gathered public comment on the adequacy of the current nutrient composition of infact formulas and whether revision of FDA's infant formula nutritional labeling regulation, 21 CFR 105.65, was necessary. The comments relevant to the proposed quality control procedure regulations which were received in response to these public proceedings are on file with the Dockets Management Branch under the docket number set forth above.

The Congress was also quick in recognizing the need for more stringent government control over these vital food products. As early as November 8, 1979, several legislative proposals, each entitled the Infant Formula Act of 1980, were introduced by various members of the U.S. House of Representatives, most notably by Messrs. Gore, Mottl, and Carter, and were referred to the House Subcommittee on Health and the Environment (Subcommittee). These proposals were intended to require a broad range regulatory scheme for infant formula products which included periodic testing, a statutory nutrient table, and recordkeeping requirements for assuring their safety and nutritional quality. Hearings on these proposals were conducted by the Subcommittee in February and March 1980. The final House bill, H.R. 6940, was considered by the Committee on Interstate and Foreign Commerce on April 16, 1980, and ordered reported by unanimous vote (see H.R. Rept. No. 96-936, 96th Cong., 2d Sess., p. 4 (May 12, 1980)).

Similar legislation to tighten regulatory control over infant formulas was introduced in the U.S. Senate by Messrs. Metzenbaum, Baucus, and Leahy on March 27, 1980. The Senate bill, S. 2490, was referred to the Committee on Labor and Human Resources (Committee). Hearings on the legislation were conducted by the Subcommittee on Health and Scientific Research on June 12 and August 5, 1980, and it adopted and accepted the House companion bill, H.R. 6940, with one amendment. On August 21, 1980, S. 2490 was ordered reported by the full Committee (see S. Rept. No. 96-916, 96th Cong., 2d Sess., p. 2 (August 26, 1980)).

Thereafter, this bill was passed by both Houses of Congress. On September 26, 1980, the President signed into law the Infant Formula Act of 1980 (Pub. L. 96-359, 94 Stat. 1190). This amendment to the Federal Food, Drug, and Cosmetic Act (the act) establishes a new section 412 (21 U.S.C. 350a) and creates a separate category of food designated as "infant formula." It requires that infant formulas meet specified standards of quality and safety. Section 412(g) of the act provides that an infant formula shall contain nutrients at specified levels in accordance with a table set forth therein. If a formula product, except for a special formula as defined in section 412(f) of the act, fails to contain the nutrients in the specified amounts, it is deemed adulterated under new section 412(a)(1)(A). In addition, if a formula, except for one defined in section 412(f), does not meet certain quality factor requirements (section 412(a)(1)(B)) or if a formula is not manufactured or processed in compliance with certain quality control procedures (section 412(a)(1)(C)), it is also deemed adulterated.

Section 412(a)(2)(D) of the new law gives the Secretary of Health and Human Services the authority to promulgate regulations* establishing:

> Such quality control procedures * * * necessary to assure that an infant formula provides nutrients in accordance with this section and establish requirements respecting the retention of records of procedures required under this clause (including maintaining necessary nutrient testing records) * * *. Quality control procedures prescribed by the Secretary shall include the

*This authority is delegated to the Commissioner of Food and Drugs, 21 CFR 5.1(a)(1).

periodic testing of infant formulas to determine whether they are in compliance with this section.

The legislative history describes the anticipated infant formula "quality control procedure" regulations in terms which encompass the entire manufacturing process:

> * * * Quality control procedures are those procedures which would assure proper manufacturing of formula products.
>
> Quality control procedures are not limited to those "good manufacturing practices" applicable to food. Quality control procedures are intended to insure that the safety and nutritional potency of a formula is built into the manufacturing process. This authority is necessary as the absence of quality control mechanisms was a major factor in the production and subsequent sale last year of two formula products critically deficient in chloride. Existing statutory authority in this area is inadequate as it is limited to assurances that infant formula is filth free and is manufactured in a sanitary facility. S. Rept. No. 96-916, 96th Cong., 2d Sess., pp. 5-6 (August 26, 1980); H.R. Rept. No. 96-936, 96th Cong. 2d Sess., pp. 6-7 (May 12, 1980).

It is therefore clear that such procedures for infant formulas are to be in addition to those procedures currently codified under the good manufacturing practice (GMP) regulations applicable to food sanitation (21 CFR Part 110) and the GMP requirements for low-acid canned foods (21 CFR Part 113).

Until the agency promulgates infant formula quality control procedure regulations, the new law requires manufacturers to test their formula products to assure their nutritional quality and safety and report to FDA every 90 days that their formulas provide nutrients required by the table in section 412(g) (see section 412(b)(1) of the act).

The Congress expected FDA to move expeditiously in proposing, promulgating, and establishing quality control procedures for the manufacturing of infant formulas. S. Rept. No. 96-916, 96th Cong., 2d Sess., p. 6 (August 26, 1980). Thus, the agency is now proposing to establish new Part 106 (21 CFR Part 106) specifying the infant formula quality control procedures. These procedures are applicable to the entire infant formula manufacturing process, from the receipt of ingredients until the finished infant formula is released for shipping.

A total quality control program for the manufacture of infant formulas is necessary to ensure that each batch of the formula is uniform in its composition and conforms to the requirements of section 412 of the act. These proposed regulations constitute a planned and systematic procedure of sampling, testing, and analysis which requires (1) an acceptance protocol for ingredients assuring that they conform to strict specifications for composition and purity; (2) an in-process operational control program of ingredient addition, blending, homogenization, and standardization; and, (3) a finished product evaluation system that specifies sampling frequency and an analytical format that defines the product release ranges at which the product may be shipped. These procedures necessarily include requirements for establishing and maintaining adequate quality control records to document that each formula meets the testing and nutrient requirements of section 412 of the act. In addition, the agency is including as a subpart to this proposal the notification format to be followed by manufacturers in reporting to FDA under those situations set forth at sections 412(b) and 412(c) of the act. Notice of these reporting procedures was published in the **Federal Register** of November 21, 1980 (45 FR 77136) and do not require public comment. The instruction to promptly notify FDA of a suspected adulteration or misbranding of an infant formula has been modified to provide for telephone notification (see § 106.130(d)) of either the Director of the appropriate FDA district office or the Emergency and Epidemiological Operations Branch in headquarters.

Status and Applicability of Quality Control Procedure Regulations

Proposed § 106.1 (21 CFR 106.1) states that the criteria set forth in proposed §§ 106.20, 106.25, 106.30, and 106.100 shall apply in determining whether the controls used in the manufacture, processing, and packing of infant formula products meet the requirements of section 412 of the act as to safety, quality, and nutritional composition. (See sections 412(a)(1)(C) and 412(a)(2)(D) of the act.) A manufacturer's failure to comply with the applicable requirements of these regulations after their effective date shall render the infant formula product adulterated under section 412(a)(1)(C) of the act, and such formula as well as the person who is responsible for the failure to comply may be subject to regulatory action. Thus, these regulations, after promulgation, will have the full force and effect of law. See *Weinberger* v. *Hynson, Wescott & Dunning, Inc.*, 412 U.S. 609 (1973); *United States v. Nova Scotia Food Products Corp.*, 568 F.2d 240 (2d Cir. 1977); *National Nutritional Foods Ass'n* v. *Weinberger*, 512 F.2d 688 (2d Cir. 1975).

Definitions

Proposed section 106.3 (21 CFR 106.3) incorporates the definitions and interpretations contained in section 201 of the act (21 U.S.C. 321), when such terms are used in these proposed regulations. Other more technical terms are defined in this proposed regulation and are based on FDA's experience in regulating foods and common usage in the infant formula industry.

Quality Control Requirements

Receipt of ingredients. Proposed § 106.20 (21 CFR 106.20) describes those procedures applicable to the receipt of infant formula ingredients which are essential for assuring that each ingredient meets its stated specifications and, therefore, assuring that the finished product conforms to section 412(g) of the act. To assure that ingredients, which contain nutrients likely to be affected by shipping, storage, or other conditions (such as an error in the mixing of nutrients by the supplier), conform to their specifications, each lot of ingredient which may be affected must be analyzed for such nutrients, or if appropriate, an indicator nutrient. An indicator nutrient is one, usually a label ingredient of a premix, the concentration of which is measured at several stages during the production of the infant formula product because it is most likely to be affected by the process. If ingredients, including nutrients and nutrient premixes, are not certified or guaranteed by the supplier or labeled as meeting prescribed standards, an extensive sampling and testing plan must be employed utilizing a statistically random sampling followed by confirmatory quantitative analysis for each nutrient required by section 412(g) of the act. The proposed section requires that an identifying number or code be used in recording the disposition of each nutrient ingredient, as examples, when they are rejected to the supplier or when they are added to a premix or batch.

In-Process Control

Proposed § 106.25 (21 CFR 106.25) describes the requirements for infant formula in-process control. Each distinct processing operation shall be entered on a batch record and its satisfactory completion recorded by the operator. A designated supervisor shall check and sign each batch record. A second person shall confirm the addition of each ingredient. Sampling the in-process batch after various additions of nutrients, analyzing the composition for uniformity and indicator nutrients, and standardizing the completed batch

assures the formula's conformity to the nutritional requirements of section 412(g) of the act.

Base Blend

Production of an in-process batch usually begins with the formulation of a base blend, generally from either milk or soy ingredients, or other sources of protein, as well as other sources of fat or carbohydrate. The base blend may also contain various electrolytes, emulsifiers, stabilizers, and other functional ingredients. FDA is proposing in § 106.25(b) that each base blend be sampled after thorough mixing and analyzed for protein, fat, ash, moisture, and carbohydrate to confirm the levels of the major components in the base blend.

Premixes

Certain infant formula ingredients such as vitamins, minerals, and amino acids are sometimes added to the in-process batch as premixes. Commonly used premixes for infant formula production generally include an oil-soluable premix and one or more water-soluble premixes. FDA is proposing in § 106.25(c) that a premix which is made from individual nutrient components by the infant formula manufacturer shall be analyzed for each nutrient prior to its addition to the base blend, unless analyses for each nutrient contributed by the premix are performed on the contents of the holding tank(s) as prescribed in proposed § 106.25(e). When a premix is analyzed for each nutrient as set forth in proposed § 106.25(c), FDA is proposing that the in-process batch be analyzed for the appropriate indicator nutrient as provided by § 106.25(d). After the addition of premixes to the base blend, the proper quantity of each premix in an in-process batch may be verified (proposed in paragraph (d)) by analyzing each in-process batch for one or more of the indicator nutrients of each of the premixes used. Unless analyses for each nutrient contributed by a premix are perfomed in-process, such analyses must be performed on the contents of the holding tank(s). If the indicatior nutrient is within the prescribed limit of specification, the other component nutrients are expected to be in the in-process batch within specification. However, selected batches of finished product in containers are to be analyzed for all nutrients specified in section 412(g) of the act (proposed in § 106.30(a), (b), and (c)).

When a nutrient ingredient is not suitable for use in the preparation of a uniform, stable premix, that nutrient is sometimes added separately to the in-process batch. FDA is proposing in § 106.25(d) to require that the presence of the proper quantity of that nutrient be verifed by analysis of each in-process batch for that nutrient, unless the analysis is later performed on samples from the holding tank(s) as prescribed in proposed § 106.25(e). After the addition of premixes and nutrients added individually, proposed § 106.25(f) requires the in-process batch to be adjusted as necessary to confrom to the batch formula.

Product in Holding Tanks

One or more in-process batches may be accumulated in a holding tank(s) to form a filling batch which then is standardized prior to further processing. FDA is proposing in § 106.25(e) to require the testing of samples from each holding tank of the product for solids, homogeneity, osmolality, and sedimentation as indicators of nutrient dispersal and consequent product uniformity. Testing for other physical attributes of infant formulas is not included in this proposed regulation because most physical attributes normally are used as a measure of the organoleptic properties of the product and do not aid in determining that nutrient levels in the product are being maintained. FDA is also proposing in § 106.25(e)(1) to (5) to require that samples taken from the holding tank be analyzed for major nutrients (protein, fat, and carbohydrate); for indicator nutrients in premixes; for each nutrient in a premix made from individual nutrient components by the infant fromula manufacturer unless analyzed prior to use; and for nutrients added independently of premixes during formulation of the product, unless analyzed in the in-process batch.

The level of testing and analyses proposed for the product in the holding tank, together with the previously discussed requirements for the sampling and analysis of ingredients and in-process product, provides the manufacturer with an increased ability to detect and correct product compositional defects prior to heat sterilization or dehydration and packaging into individual containers. For those nutrients that are heat-labile, appropriate indicator nutrients shall be checked after heat processing or dehydration to assure their adequacy in the finished product (proposed in § 106.30(b)(1)(ii)). In this manner, an increased level of assurance of finished product integrity is attained at the earliest possible time in the porcess, thus averting expensive finished product rework or recall if distributed. At the same time, a decreased level and frequency of sampling and analysis of finished product after processing and packaging is required.

Release of Product for Heat Sterilization or Dehydration

FDA proposes in § 106.25(f) that if the product in each holding tank conforms to its specifications, it may be released for subsequent heat sterilization or dehydration and packaging. Otherwise, it shall be adjusted and reanalyzed to verify the efficacy of standardization.

Finished Product Analyses Prior to Shipment

FDA proposes in § 106.30 (21 CFR 106.30) that random samples of product taken after heat sterilization or dehydration and packaging be tested for physical attributes and analyzed for indicator nutrients that measure possible product damage before the product is released from the manufacturer's control. FDA is proposing product analysis for indicator nutrients that measure possible damage because certain nutrients that are sensitive to heat, light, oxygen, pH, or a combination thereof may be affected by the manufacturing processes. Trace minerals, such as copper and iron, and enzymes may catalyze these effects. Heating and/or the presence of reducing sugars may degrade protein quality by decreasing the biological availability of certain essential amino acids of the protein. The indicator nutrient(s) selected to measure process damage in any formulation must be the nutrient(s) most susceptible to process damage.

When two or more nutrients are equally suitable to fulfill an indicator role, the complexity and cost of the analytical methods for these nutrients are additional factors affecting the selection decision. In addition, the same nutrient may be adequate to fulfill more than one indicator role, simplifying part of the control process. Thus, vitamin A may serve as an indicator of the oil-soluble premix addition to the in-process batch and as a measure of process damage in the finished product.

When the history of nutrient stability gathered during product development indicates that a satisfactory indicator nutrient level gives assurance of proper levels of nutrients similar to the indicator, the product may be shipped if the result of that analysis is satisfactory.

Finished Product Analyses of Selected Batches

FDA proposes in § 106.30(b) a three-tiered staggered analyses program for finished formula products. While samples of the finished product must be monitored for all nutrients required by

section 412(g) of the act and those claimed on the label, the timeframe for analyses is not uniform for all nutrients. FDA believes that less frequent analyses for certain nutrients are reasonable; many require a longer time to analyze than other nutrients that can satisfactorily serve as indicators. There are no documented cases of deficiencies in normal infants of biotin, choline, and inositol. Vitamins D and K are well retained in the human body; vitamin D also is highly stable in infant formulas, while vitamin K intake in infants other than newborns is usually augmented by intestinal bacterial production of this vitamin. The vegetable oils now used as fat sources are rich in linoleic acid. Protein efficiency ratio (PER) and tryptophan (the content of which may be used in meeting the niacin requirement in section 412(g) of the act) are not expected to vary unless there is a change in the protein ingredients or processing procedures, at which time an analysis of these components is required.

Although thickening and stabilizing agents may be added to infant formulas to maintain the consistency and to prolong the stability of the product over its shelf life, there may be some changes in consistency and nutritional qualities during storage. Therefore, FDA is proposing in § 106.30(b)(3) that samples from selected filling batches be checked at 3 month intervals throughout the shelf life of the product to ascertain its stability and nutritional adequacy. Scheduling a bioanalysis of vitamin D and the biological evaluation of PER to occur over a 6-month cycle rather than every 3 months is considered appropriate because of the length of time required to complete the bioanalysis.

Criteria for accepting and rejecting a product

FDA is proposing in § 106.30(c) that the ranges of nutrient composition in the finished product shall be such that their lower limits do not fall below, and their upper limits do not exceed, the minimum and maximum levels, respectively, specified in section 412(g) of the act and that the composition shall be consistent with label declarations. To assure that the upper and lower levels of the listed nutrients in the act are met, proposed § 106.30(d) requires the establishment of an appropriate finished product acceptance/rejection system based on statistical quality control criteria. The proposal further requires that when the results of testing three consecutive filling batches show a trend in deviations from specified ranges in one or more nutrients, the product shall be evaluated to ascertain and implement steps that need to be taken to maintain the product in conformity with section 412(g) of the act.

Changes in Ingredients or Processes

FDA proposes in § 106.30(e) that an infant formula manufactured after changes in the formulation or processing has occurred must be controlled more stringently than products manufactured without such changes. To assure the adequacy of the nutrient composition of formulas manufactured after a change in formulation or processing has occurred, FDA is proposing that a manufacturer be required to evaluate the effects of changes in ingredients or processing conditions in the first and last of the first 10 filling-batches together with product from any 2 of the other 8 filling batches. As set forth in proposed § 106.30(e)(1), if the changes in formula are minor (e.g., changing ingredients from one supplier to another whose products differ only in minor aspects from those previously used), composite samples are to be analyzed for all nutrients changed and for those nutrients affected by the change. As set forth in proposed § 106.30(e)(2), if the changes in formulation are major (e.g., changing type of ingredients, such as soy flour to soy isolate, or replacing a heat exchanger with a steam injector-vapor tank system), a complete analysis of all required nutrients and of PER is to be performed on the 1st and 10th filling batches as well as on any two of the other eight filling batches, except that analyses for linoleic acids, vitamin D, vitamin K, choline, inositol, biotin, PER, and tryptophan (if necessary as part of the declaration of niacin equivalents) need be made only on the 1st and 10th batches if they meet specifications. These detailed analyses are necessary to further assure nutritional adequacy, i.e., that the premix system is functioning as intended, and that no unexpected losses of nutrients are occurring during processing.

Coding

The coding of food products is necessary and important in ascertaining positive lot identification. Positive lot identification facilitates the identification, the segregation, and the traceability of contaminated products or products that may be otherwise unfit for their intended use. Congress has recognized the utility of this type of product coding, as have many members of the food industry, who have developed guidelines for their segments of the industry. The courts too recognized the self-evident rationality of the coding of food products. See *National Confectioner Ass'n* v. *Califano*, 569 F.2d 690, 695 (D.C. Cir. 1978).

In addition, Congress has reemphasized in the Infant Formula Act of 1980 the importance of the concepts of coding and traceability for infant formulas by requiring each infant formula manufacturer to make and retain necessary records respecting the distribution of the infant formula through any establishment owned or operated by such manufacturer as may be necessary to effect and monitor a recall of the formula. (See section 412(e)(1) of the act). Accordingly, FDA is proposing in § 106.90 (21 CFR 106.90) to require the manufacturer to place permanent and conspicuous legible coding marks on each infant formula package delivered or displayed to pruchasers, so that such code marks can be easily seen on the unopened package. The marks must identify at a minimum, the establishment where the formula is packed, the product that is contained therein, the year and day and product that is packed, and the period during which, the product is packed. Further, FDA is proposing that the packing period code be changed with sufficient frequency to enable the identification of a period of time when certain personnel were on duty and in-plant conditions were relatively constant.

Records and Reports

The Infant Formula Act of 1980 expanded the agency's inspectional authority in section 704 of the act (21 U.S.C. 374), by permitting duly authorized FDA employees to have access to and to copy and verify any records bearing on whether any infant formula meets the requirements of section 412 of the act. Thus, FDA is proposing in § 106.100 (21 CFR 106.100) that infant formula manufacturers maintain: (a) Records of the results of examinations or copies of supplier guarantees or certifications verifying that the raw materials, packing materials, and infant formulas comply with section 412 of the act and with FDA regulations, guidelines, or action levels, and (b) those quality control procedure records, including in-process and finished product testing records, necessary to show that the nutrient content of infant formulas meets the requirements of section 412 of the act. FDA proposes that these records be kept for a period of time that meets or exceeds the shelf life of the product.

Notification

FDA is including as subpart D to the proposed quality control procedure regulations (proposed §§ 106.120, 106.122, and 106.130; 21 CFR 106.120,

106.122, and 106.130) the notification procedures and format to be followed by manufacturers in reporting to FDA as required by sections 412(b) and 412(c) of the act. Notice of these reporting procedures was published in the **Federal Register** of November 21, 1980 (45 FR 77136) to advise manufacturers of the reporting requirements in new section 412 of the act and to inform them of how to notify the agency and which offices at FDA to submit the required reports.

In that notice, the agency included the reporting requirement of section 412(b)(1) of the act, which directs manufacturers to notify FDA within 90 days following the date of enactment of the Infant Formula Act and on each 90th day thereafter, that each "existing" infant formula produced by a manufacturer provides nutrients required by section 412(g) of the act. Because this reporting requirement expires on the effective date of these proposed quality control procedure regulations, the agency is not including the format for the section 412(b)(1) reporting requirement herein. In addition, the reporting format in § 106.122 for reformulations as required by section 412(b)(3) of the act, has been modified to include a short description of the change(s) in formulation; and the telephone notification in § 106.130(d) has been modified to give the manufacturer the option of contacting either the appropriate FDA District Director or the FDA Emergency and Epidemiological Operations Branch. However, all other reporting formats required by section 412(b) and (c) of the act will continue to be applicable and are therefore being included in these proposed regulations. Because these notification requirements are not substantive and reflect only a statutory interpretation of section 412(b) and (c), public comment is not required.

Clinical Testing

FDA recognizes that premarket clinical evaluation in humans may be appropriate whenever certain changes affecting the nutritional profile of an infant formula are made, particularly in the case of new or reformulated products. FDA also recognizes that the degree and complexity of clinical testing would vary according to the extent of the changes in the formula. The testimony that was received during the February 19, 1980, public meeting was supportive of the need for clinical trials in appropriate situations and indicated that the infant formula industry now makes ad hoc decisions to clinically evaluate formulas based upon recommendations of physicians and nutritionists. However, the discussion provided at the public meeting was not sufficiently specific to constitute a basis for the development of an FDA policy on clinical testing of infant formulas. A copy of the testimony received at the public meeting concerning infant formula clinical testing is on file with the Dockets Management Branch under the docket number set forth above.

FDA also requested recommendations from the Committee on Nutrition of the American Academy of Pediatrics (CON/AAP) on clinical testing of infant formulas. In a statement on June 23, 1980, CON/AAP reported to FDA that clinical testing of new and reformulated products is considered advisable from time to time, and is now carried out in established clinical research centers with the collaboration of technical experts, nutrition scientists, and pediatricians. CON/AAP recommended that, in view of the existing practices governing nutrient content and manufacturing procedures, no regulations be devised for infant formula clinical testing. This recommendation was based on three reasons: (1) Problems with the manufacture of infant formulas have been exceptionally rare in the past; (2) future modifications of infant formulas that are justified nutritionally or economically cannot be wholly predicted, and no simple code can govern all anticipated eventualities; and, (3) future clinical trials will have to be adapted to the evolving ethical codes governing research on infants. A copy of the CON/AAP statement with accompanying background information on infant formula regulations is also on file with the Dockets Management Branch.

Considering the complexities surrounding clinical testing of infant formulas in infants and the fact that such testing is currently an integral part of the manufacturer's development of new formulas, FDA is not now proposing regulations on clinical testing of infant formulas. However, the agency is soliciting public comment on the need for establishing a policy or regulation on clinical testing of infant formulas. Answers to the following questions are essential to the development of an agency policy, and comments thereon are requested: (1) What constitutes a new infant formula, and what constitutes major reformulations of existing formulas that would require clinical testing; (2) what constitutes adequate metabolic testing, growth and development studies, or acceptance and tolerance tests, and in what situations are each of these types of testing appropriate; and (3) what criteria should be used to evaluate the results of tests or to measure the effectiveness (performance) of an infant formula? Although responses to these specific questions are especially desired, comments on any aspect of clinical testing of infant formulas are welcomed. All comments received will be considered by FDA in determining its future course of action with respect to clinical testing of infant formulas.

FDA proposes that all affected products initially introduced into, or initially delivered for introduction into, interstate commerce or prepared from raw materials shipped in interstate commerce on or after 180 days after date of publication in the **Federal Register** of any final regulation adopted on the basis of this proposal, shall comply with that regulation.

The agency has determined under 21 CFR 25.24(d)(13) (proposed December 11, 1979 (44 FR 71742)) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 412, 701(a), 52 Stat. 1055 as amended, 94 Stat. 1190 (21 U.S.C. 350a, 371(a))), and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), it is proposed that Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 106 to read as follows:

PART 106—INFANT FORMULA QUALITY CONTROL PROCEDURES

Subpart A—General Provisions

Sec.

106.1 Status and applicability of the quality control procedure regulations.
106.3 Definitions.

Subpart B—Quality Control Procedures for Assuring Nutrient Content of Infant Formulas

106.20 Ingredients receipt.
106.25 In-process control.
106.30 Finished product evaluation.
106.90 Coding.

Subpart C—Records and Reports

106.100 Records.

Subpart D—Notification Requirements

106.120 New formulations.
106.122 Reformulations.
106.130 Notification format.

Authority: Secs. 412, 701(a), 52 Stat. 1055 as amended, 94 Stat. 1190 (21 U.S.C. 350a, 371(a)).

Subpart A—General Provisions

§ 106.1 Status and applicability of the quality control procedure regulations.

(a) The criteria set forth in §§ 106.20, 106.25, 106.30, 106.90, and 106.100 shall apply in determining whether the controls used in the manufacturing, processing, and packing of infant formula products meet the requirements of section 412 of the act as to safety, quality, and nutritional composition.

(b) The failure to comply with any regulation set forth in §§ 106.20, 106.25, 106.30, 106.90, and 106.100 applicable to the manufacturing, processing, and packing of an infant formula shall render such formula adulterated under section 412(a)(1)(C) of the act, and such formula, as well as the person who is responsible for the failure to comply, may be subject to regulatory action.

(c) The requirements set forth in this part are to be implemented and followed by any person who is a manufacturer of an infant formula.

(d) If a person engages in only some operations subject to the regulations in this part and not others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

§ 106.3 Definitions.

The definitions and interpretations contained in section 201 of the act are applicable to such terms when used in this part. The following definitions shall also apply:

(a) *Filling batch.* A filling batch is one or more in-process batches combined in a holding tank(s) and standardized for filling into finished product containers over a prescribed filling time.

(b) *Ingredients.* Ingredients are all substances, including the required nutrients specified in section 412(g) of the act, which are necessary for the manufacture of an infant formula product.

(c) *Indicator nutrient.* An indicator nutrient is a nutrient, usually one ingredient of a premix, the concentration of which is measured at several stages during the manufacturing of the infant formula product to confirm one or both of the following characteristics or operations:

(1) Proper addition and proper distribution of premix in the in-process batch and in the holding tank; and

(2) Stability of labile nutrients during production, e.g., vitamin A, vitamic C.

(d) *In-process batch.* An in-process batch is a combination of ingredients, including the base blend, premixer and other nutrients in accordance with a manufacturing order at any point in the process prior to packaging.

(e) *Manufacturer.* A manufacturer is a person that prepares, reconstitutes, or otherwise changes the phycical or chemical characteristics of an infant formula as defined in section 201(aa) of the act and packages the product in a container for distribution.

(f) *Nutrient.* A nutrient is any vitamin, mineral, or other substance required by section 412(g) of the act.

(g) *Nutrient premix.* A nutrient premix is a combination of two or more nutrients which is added as a single ingredient during processing.

Subpart B—Quality Control Procedures For Assuring Nutrient Content of Infant Formulas

§ 106.20 Ingredients

(a) Manufacturers shall ensure that incoming ingredients are not used in the manufacture of infant formulas if they have visable shipping damage or other defects or their label does not comport with order specifications. An identifying number or code shall be used in recording the disposition of each nutrient ingredient.

(b) Ingredients, other than nutrient premixes, which are generally stable in shipping and storage, and which are received under a supplier's guarantee or certification, or are labeled as having compositions complying with specifications in the U.S. Pharmacopeia, the National Formulary, the Food Chemicals Codex, or other similar recognized standards, may be forwarded without analysis for manufacturer use.

(c) When the nutrient(s) in an ingredient is likely to be affected by shipping or storage conditions, it shall be sampled and analyzed by the manufacturer. The ingredients shall be sampled by taking statistically randomized subsamples and a composite of the subsamples shall be analyzed quantitatively for each such nutrient or nutrients.

(d) Nutrient premixes which have been guaranteed or certified by the supplier shall be sampled and analyzed by the manufacturer. Such a premix shall be sampled by taking statistically randomized subsamples, and a composite of the subsamples shall be analyzed quantitatively for an indicator nutrient.

(e) Where ingredients, including individual nutrients or nutrient premixes, are without a supplier's guarantee or certification, or are not labeled as complying with prescribed standards, each lot shall be sampled and analyzed by the manufacturer. Each lot shall be sampled by taking statistically randomized subsamples to give a composite sample for confirmatory quantitative analysis for each nutrient. The samples shall be analyzed by recognized methods, such as those in the current "Official Methods of Analysis of the Association of Official Analytical Chemists," including a chemical method for vitamin D unless otherwise specified in this regulation. If found to be within specifications, the ingredients may be forwarded for manufacturing use.

(f) Lots that are not within specifications shall be conspicuously marked by the manufacturer that they have been rejected and shall be removed to a restricted area pending disposition.

§ 106.25 In-process control.

(a) An appropriate formula based on the composition of the ingredients and prepared for each in-process batch shall be checked and signed by a quality control supervisor. Each ingredient of the batch, and the amount and place of entry of the ingredient into the process, shall be listed on a batch record. Operators shall initial each entry of an ingredient into the process and record nutrient ingredient identification numbers on the batch record. This record shall accompany the batch while in-process and each entry on it shall be initialed by a second person for verification of the kind and the amount of the ingredient. The batch record shall be filed with all processing control records associated with the batch.

(b) A base blend, prepared by mixing the appropriate ingredients, including sources of protein, fat, and carbohydrate with filtered, potable water of quality mandated by the local Public Health Agency shall be thoroughly mixed and sampled by the manufacturer. A proximate analysis for protein, fat, ash, moisture, and carbohydrate shall be performed by the manufacturer on samples from each base blend.

(c) A premix that is made from individual nutrients by the infant formula manufacturer shall be analyzed by such manufacturer for each nutrient prior to its addition to the base blend, unless analyses for each nutrient contributed by the premix are performed on the contents of the holding tank(s) as prescribed in paragraph (e) of this section.

(d) After the addition of the nutrient premixes to the base blend, and homogenization, when appropriate, the inprocess batch may be sampled and analyzed for the apropriate indicator nutrient of each premix (e.g., vitamin A for the oil-soluble premix, vitamin C for the water-soluble vitamin premix, and manganese for the mineral premix). If a

nutrient is not suitable for use in the preparation of a uniform, stable premix, or if the composition of the nutrient is altered significantly with ensuing processing, it may be added separately at the most advantageous point in the manufacturing process to ensure its presence in prescribed amounts in the finished product. After the addition of such nutrient, the in-process batch may be analyzed for each individual added nutrient. Unless specified nutrient analyses are performed in-process, they shall be performed on the contents of the holding tank(s) as prescribed in paragraph (e) of this section.

(e) The manufacturer shall accumulate in-process batches in the holding tank(s) from which each filling batch is to be drawn. Each filling batch shall be held in storage until the nutrient composition of the contents of each holding tank is verified. After mixing, samples from each holding tank shall be analyzed by the manufacturer for the following physical attributes and nutrients:

(1) Solids, homogeneity, osmolality, and sedimentation.

(2) Protein, fat, and carbohydrate.

(3) Indicator nutrient(s) for premixes.

(4) Each nutrient in a premix made from individual nutrent components by the infant formula manufacturer and not analyzed in the in-process batch.

(5) Nutrients added independently of premixes during formulation of the product if not analyzed in the in-process batch.

(f) If the formula product in each holding tank conforms to its specifications, it may be released for heat sterilization or dehydration and packaging; otherwise it shall be adjusted as required and reanalyzed to verify the efficacy of standardization.

§ 106.30 Finished product evaluation.

(a) The manufacturer shall take random samples of the finished formula product from each packaging line after heat sterilization or dehydration and packaging, to represent the entire filling batch (i.e., from the start of the first holding tank to the end of the last holding tank).

(b) A sufficient number of containers shall be taken by the manufacturer to provide adequate product for the following types of testing:

(1) *Immediate analysis.* A composite sample of three containers taken randomly over each 2-hour period at each packaging line for each filling batch shall be analyzed before shipping for:

(i) Solids, homogeneity, osmolality, and sedimentation.

(ii) Indicator nutrients to assess process damage, such as vitamin A, vitamin B_1, vitamin B_6, and vitamin C.

(2) *Extended analysis.* Replicate samples of containers for the immediate analyses, as described in paragraph (b)(1) of this section, are to be taken from the first of every 10 filling batches or taken semi-monthly, whichever comes first. These samples shall be analyzed for the content of reducing sugar and all nutrients specified in section 412(g) of the act and declared on the label, except linoleic acid, vitamin D, vitamin K, choline, inositol, biotin, tryptophan (if necessary as part of the declaration of niacin equivalents), and those which were tested in the immediate analyses.

(3) *Progressive analysis.* Using replicates of the samples collected from one filling batch as specified in paragraph (b)(2) of this section, and beginning 3 months after their packaging, progressive analysis shall be initiated on a new filling batch every 3 months. These samples shall be analyzed every 3 months throughout the shelf life of the product for physical attributes (i.e., solids, homogeneity, osmolality, and sedimentation), and for all nutrients declared on the label. Vitamin D may be determined by chemical methods, except that it and the protein efficiency ration (PER) shall be determined by the appropriate AOAC bioassay method of analysis once every 6 months throughout the shelf life of the product.

(i) The rat bioassay method for determining vitamin D shall be the method prescribed in "Official Methods of Analysis of the Association of Official Analytical Chemists," 13th ed. (1980), secs. 43.195–43.208 "Vitamin D (30)—Official Final Action,"[1] which is incorporated by reference.

(ii) The method for determining biological quality of protein in terms of PER shall be the method prescribed "Official Methods of Analysis of the Association of Official Analytical Chemists," 13th ed. (1980), sections 43.212–43.216 "Biological Evaluation of Protein Quality (Protein Efficiency Ratio) (32)—Official Final Action,"[1] which is incorporated by reference.

(c) Solids, homogeneity, osmolality, and sedimentation shall conform to release ranges established by the manufacturer. Ranges of the nutrient composition in the finished product shall be such that their lower limits do not fall below, and their upper limits do not exceed, the minimum and maximum levels, respectively, specified in section 412(g) of the act, and the composition shall be consistent with label declarations.

(d) To ensure that the infant formula product contains those nutrients and levels of nutrients set forth in section 412(g) of the act, the manufacturer shall establish controls which shall include the implementation of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures based upon the design and capability of the manufacturing process. The manufacturer shall also establish acceptance criteria for sampling and testing to ensure that batches of infant formula meet nutrient specifications and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance, warning, and rejection ranges.

(1) The acceptance ranges lie within the upper and lower control limits of a statistical process average having two standard deviations as the limit boundaries. Where a nutrient level is between the second and third standard deviation, corrective measures shall be taken to bring the product into the acceptance range.

(2) If in any composite sample, any nutrient level lies below the three standard deviation limit, or the level of any nutrient having a maximum allowable concentration specified in section 412(g) of the act is above the three standard deviation limit, the filling batch shall be rejected and disposed of unless it is reconditioned and brought within specifications.

(3) When the results of testing three consecutive filling batchs show a trend in deviations from specified ranges in one or more nutrients, the product shall be evaluated to ascertain the steps needed to be taken to maintain the product in conformity with section 412(g) of the act.

(e) The manufacturer shall perform analyses for evaluation of the effect of changes in ingredients or processing conditions which could affect the physical attributes or nutrient levels as indicated in paragraph (e)(1) and (2) of this section. Three samples (each consisting of a composite sample representing the beginning, the middle, and the end of the filling batch) shall be taken from each of the first 10 filling batches for evaluation prior to shipment of finished products to determine the effects of such changes which include, but are not limited to:

(1) Minor changes in ingredients (e.g., changing one or more ingredient levels

[1] Copies may be obtained from the Association of Official Analytical Chemists, P.O. Box 540, Benjamin Franklin Station, Washington, DC 20044, or examined at the Office of the Federal Register Library.

to bring the ranges of nutrient concentration more closely within prescribed release limits; changing ingredients from one supplier to another whose products differ only in minor aspects from those previously used; changing the water source). The composite samples from the first and tenth filling batches and from two additional filling batches chosen from filling batches two through nine shall be analyzed by the manufacturer for all nutrients changed and those affected by the change.

(2) Major changes of ingredients more significant than those described in paragraph (e)(1) if this section, or changes in processes involving equipment or conditions such that physical attributes will be affected or labile nutrients will degrade beyond previously experienced ranges (e.g., changing type of ingredients, such as soy flour to soy isolate; replacing a heat exchanger with a steam injector-vapor tank system; changing time-temperature conditions of preheating during formulation of product; changing mixing times or mixing temperatures; or changing holding times and temperatures of sterilization). A complete analysis of all nutrients required by section 412(g) of the act and of PER shall be performed by the manufacturer on the composite samples from the first and tenth filling batches; analyses of all such nutrients and PER also shall be made on the composite samples from two additional filling batches chosen from filling batches two through nine, except that analyses for linoleic acid, vitamin D, vitamin K, choline, inositol, biotin, PER, and tryptophan (if necessary as part of the requirement of niacin) need not be made if they are within specification in filling batches 1 and 10.

§ 106.90 Coding.

The manufacturer shall mark each container of a finished infant formula with a conspicuous, permanent, and legible identifying code. Code marks shall be visible to purchasers on unopened packages. The required code shall identify the establishment where packed, the product contained therein, the year packed, the day packed, and the period during which packed. The packing period code shall not extend over a period of more than one personnel shift.

Subpart C—Records and Reports

§ 106.100 Records.

(a) Records of results of examinations and copies of suppliers' guarantees or certifications that verify compliance with FDA regulations, guidelines, or action levels for raw materials, food-packaging materials, and infant formulas shall be maintained by the manufacturer.

(b) Quality control procedure records necessary to ensure nutrient content of infant formulas, including periodic nutrient testing, shall be maintained by the manufacturer and shall contain sufficient information to permit a public health evaluation of any batch of infant formula.

(c) The records required by paragraphs (a) and (b) of this section shall be retained for a period of time that meets or exceeds the shelf life of the infant formula.

Subpart D—Notification Requirements

§ 106.120 New formulations.

The manufacturer shall notify FDA, not later than the 90th day before the first processing of any new infant formula for commercial or charitable distribution for human consumption, that the new infant formula provides the nutrients required by section 412(g) of the act and that the processing meets the quality control procedure requirements prescribed by the Food and Drug Administration and that the infant formula is not adulterated or misbranded within the meaning of the act.

§ 106.122 Reformulations.

The manufacturer, before the first processing of any infant formula produced for commercial or charitable distribution for human consumption, when the manufacturer determines that a change in its formulation or a change (as described in section 412(b)(3) of the act) may affect whether the formula is adulterated, shall notify FDA of such changes, including a description of the changes, and that the reformulated formula provides the nutrients required by section 412(g) of the act.

§ 106.130 Notification format.

(a) The notification requirements prescribed in §§ 106.120 and 106.122 of this subpart are to be submitted to FDA in the following format:

Please Type or Print all Entries

1. Enter the name of the product: _____

2. Check whether the identified infant formula is a "new formulation" _____ or a "reformulation" _____

If the identified formula is a reformulation, provide: a. A description of the change(s) in the formulation and/or processing.

b. How this (these) change(s) may affect whether the formula is adulterated.

3. Enter establishment name and address.

Name:_____
Address: _____

(City) (State) (Zip Code)

4. If establishment has a parent company, enter parent company name and address. If not applicable, check N/A.

Name:_____
Address: _____

(city) (State) (Zip Code)
N/A: _____

5. Notification Statement of the Quality of the Identified Infant Formula:

"I hereby notify FDA that the infant formula identified above meets the nutritional requirements of section 412(g) of the Federal Food, Drug, and Cosmetic Act, that the processing of the infant formula meets the quality control procedure requirements prescribed by the Food and Drug Administration and that the infant formula is not adulterated or misbranded within the meaning of said act.

Signed: _____
Date: _____

(This notification shall be signed and dated by a responsible official.)

(b) The notification requirements prescribed in paragraph (a) of this section shall be submitted to Chief, Regulatory Affairs Staff (HFF–204), Bureau of Foods, Food and Drug Administration, 200 C St., SW., Washington, D.C. 20204.

(c)(1) The manufacturer should submit to FDA one label for each infant formula produced for commercial or charitable distribution for human consumption with its submission for new formulations and reformulations.

(2) All labels are to be submitted to Chief, Regulatory Affairs Staff (HFF–204), and in accordance with the due dates established in §§ 106.120 and 106.122.

(d) The manufacturer shall promptly notify FDA when there is an infant formula in the marketplace which may not provide the nutrients required by section 412(g) of the act or when there is an infant formula otherwise adulterated or misbranded within the meaning of the act and presents a risk to human health. Descriptions of the known or suspected adulteration or misbranding must be provided. This notification shall be made, by telephone, either to the Director of the appropriate FDA district office specified in 21 CFR 5.115 or to FDA's Emergency and Epidemiological Operations Branch at 301–443–4667. After normal business hours (8 a.m. to 4:30 p.m.) the FDA emergency number, 202–737–0448, shall be used. This telephone notification shall be followed promptly by written confirmation which is to be sent to the Division of Regulatory Guidance (HFA—310), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, and to the

appropriate FDA district office specified in 21 CFR 5.115.

Interested persons may, on or before March 2, 1981, submit to the Dockets Management Branch (formerly the Hearing Clerk's office) (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Orders 12044, as amended by Executive Order 12221, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Dockets Management Branch, Food and Drug Administration.

Dated: December 22, 1980.

Joseph P. Hile,

Associate Commissioner for Regulatory Affairs.

[FR Doc. 80–40507 Filed 12–29–80; 8:45 am]

BILLING CODE 4110–03–M